

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/12, 31/19, 31/70, 31/715, A61L 25/00		A1	(11) International Publication Number: WO 98/33479 (43) International Publication Date: 6 August 1998 (06.08.98)
(21) International Application Number: PCT/IE98/00003 (22) International Filing Date: 30 January 1998 (30.01.98) (30) Priority Data: 970062 30 January 1997 (30.01.97) IE		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DE (Utility model), DK, DK (Utility model), EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(71) Applicant (for all designated States except US): ALLTRADE FINANCIAL INVESTMENTS LIMITED [IE/IE]; 87 Quinns Road, Shankhill, County Dublin (IE). (72) Inventors; and (75) Inventors/Applicants (for US only): SANTAR, Ivan [CZ/CZ]; Travniky 1006, 6602 Predklasteri (CZ). KISS, Frantisek [CZ/CZ]; Bednarova 20a, 619 00 Brno (CZ). BRIESTENSKY, Jiri [CZ/CZ]; Skolska 413, 503 43 Cernilov (CZ). (74) Agents: O'BRIEN, John, A. et al.; John A O'Brien & Associates, Duncairn House, 3rd floor, 14 Carysfort Avenue, Blackrock, County Dublin (IE).			

(54) Title: HAEMOSTATIC AEROSOL COMPOSITION

(57) Abstract

A haemostatically active aerosol composition comprises from 0.005 to 0.25 parts by weight of microdispersed polyanhydroglucuronic acid and/or salts thereof and from 0.75 to 0.005 parts by weight of a dispersing/propellant system. The system includes liquids which are non-polar or of low polarity with a surface tension of less than 30 mN/M and a permittivity at 10 kilohertz of less than 10. One example of such a system is isopentane and dimethylether.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

HAEMOSTATIC AEROSOL COMPOSITION

The invention relates to a composition of polyanhydroglucuronic acid (PAGA) and its salts. The term polyanhydroglucuronic acid and salts thereof as used herein includes copolymers thereof, especially with anhydroglucose.

Introduction

Wounds occurring in human and veterinary practice often involve minor lesions such as cuts, excoriations, burns, scalds, and various kinds of open efflorescences be it of eczematous or bacterial origin. Such lesions require rapid covering to arrest bleeding, to disinfect the wound area, and to suppress secondary microbial contamination.

It is widely accepted that the healing essentially consists of three stages which may be simply defined, as: inflammatory/exsudative phase (Phase 1), proliferative phase (Phase 2), differentiation phase (Phase 3).

It is especially important for the healing process to arrest bleeding and to suppress secondary microbial contamination of the wound. Through infiltration of the exsudate, the wound is supplied with leucocytes, neutrophilic granulocytes and monocytes, subsequently being converted to macrophages. Insufficient treatment of even minor lesions may thus give way to massive infections and to considerable complications of the healing process.

The haemostatic effect of oxidised cellulose, introduced into health care practice by pioneering work of Kenyon, Nevell, Rogovin, Jasnitzky and others, has been known since the 1940's. The oxidised cellulose is prevailingly manufactured in the form of woven or knitted tissue (such as Surgicel or Interceed by Johnson & Johnson, USA). Its application is therefore mostly limited to specialised institutions such as surgical clinics or ambulances. Also, the existing products

have certain contraindications due to their relatively high acidic character. Another disadvantage of the existing products is due to the fact that opening of the sterile packaging outside a sterile area may bring about bacterial contamination of both the sterile product and the wound; the same problem of course applies even to powder form packaged and sterilised in e.g. plastic bottles.

A detailed discussion regarding polyanhydroglucuronic acid and salts thereof is included in our co-pending Patent Application having the same date of filing as this application.

10

Pressurised aerosol packagings have been available from the 1930's, originally as insect sprays also used during World War II, using chlorofluoroalkanes as the propellant gas. They have been applied to pharmaceutical products since the 1950's, and there has been considerable development towards other types of propellants - less depleting the ozone layer and less contributing to global warming - in the last decades. However, there is no awareness of an aerosol packaged hemostatic of the polyanhydroglucuronic acid type prepared on the basis of oxidised cellulose as yet.

20

It is therefore the aim of the present invention to provide a product based on polyanhydroglucuronic acid and its salts for use as a sterile absorbable local hemostatic for mass usage by both layman and professional public, enabling easy and rapid application in common wounds and lesions and minimising detrimental effects on the environment.

25

Statements of Invention

According to the invention, there is provided a haemostatically active aerosol composition comprising from 0.005 to 0.25 weight parts of microdispersed/microdispersable polyanhydroglucuronic acid and/or salts thereof and from 0.75 to 0.995 weight parts of a suitable dispersing/propellant system.

30

The term polyanhydroglucuronic acid and salts thereof includes copolymers thereof, especially with anhydroglucose.

5 The haemostatically active aerosol composition of the invention enables easy and rapid administration and ensures permanent readiness for use, sterility at repeated application, and increased stability due to exclusion of air and UV light access to the product in a pressurised aerosol packaging.

10 The composition may include at least one pharmaceutical adjuvant which may be selected from one or more substances having suitable anti-microbial, anti-viral, anti-mycotic and/or anti-parasitic effects.

15 In one embodiment of the invention, the stable microdispersed polyanhydroglucuronic acid and/or salts thereof have the form of particles of 0.1 to 80 μ m preferably 5 to 15 μ m, in size.

20 In one embodiment of the invention, the propellant used comprises aliphatic and/or alicyclic hydrocarbons with a number of carbon atoms from 1 to 6 and/or aliphatic ethers and/or fluorinated and/or perfluorinated aliphatic hydrocarbons and/or ethers, and/or carbon dioxide and/or nitrogen and/or rare gases and, as the case may be, other auxiliary substances.

25 The polyanhydroglucuronic acid salts are preferably selected from calcium, magnesium, sodium and/or potassium salts.

30 The polyanhydroglucuronic acid and/or salts thereof are preferably prepared by a method wherein a polyanhydroglucuronic acid-containing material is subjected to partial or complete hydrolysis and neutralisation in an oxidative environment, the hydrolystate undergoing fractional coagulation to form a stable microdispersed product.

This method provides stable polyanhydroglucuronic acid and salts thereof in essentially a single process carried out in a single vessel.

Preferably the hydrolysis is carried out in an aqueous solution of inorganic and/or organic salts and/or bases. Most preferably the inorganic and/or organic salts and/or bases used for hydrolysis are chlorides, sulphates, carbonates, formates, or acetates of alkali and/or alkaline earth metals, hydroxides of alkali and/or alkaline earth metals, alkylamines, or alkanolamines, in concentrations ranging from 1 to 10^{-3} to 5 mol/l.

10

In an especially preferred embodiment of the invention the oxidative environment during hydrolysis is established by the presence of agents selected from one or more of hydrogen, sodium or magnesium peroxide, peroxyacides and their salts, hypochlorites and chlorites.

15

Preferably the procedure is carried out at a pH of from 1 to 12, and preferably, at a temperature of from 0 to 100°C.

20
25

In a preferred embodiment of the invention the polyanhydroglucuronic acid-containing material is obtained by oxidation of a suitable polysaccharide, such as native or regenerated cellulose or starch.

25

The polyanhydroglucuronic acid and salts thereof preferably containing in their polymeric chain from 8 to 30 per cent by weight of carboxyl groups, at least 80 per cent by weight of these groups being of the uronic type, at most 5 per cent by weight of carbonyl groups, and at most 0.5 per cent by weight of bound nitrogen.

Preferably the product contains at most 0.2 per cent by weight of bound nitrogen in the polymeric chain.

30

In a preferred embodiment of the invention the molecular mass of the polymeric chain is from 1×10^3 to 3×10^5 Daltons, most preferably from 5×10^3 to 1.5×10^5 Daltons.

5 The content of the carboxyl groups is in the range of from 12 to 26 per cent by weight and at least 95 per cent of these groups are of the uronic type.

10 In a particularly preferred embodiment of the invention the product contains at most 1 per cent by weight of carbonyl groups. Typically the carbonyl groups are intra- and intermolecular 2,6 and 3,6 hemiacetals, 2,4-hemialdals and C2 - C3 aldehydes.

Because neutralisation and refining is carried out in a single operation the process is cost effective.

15 As the product is in a microdispersed form there is enhanced sorption and greater accessibility for blood. Therefore the biological availability is increased and a rapid onset of haemostasis. We have also observed that the product also assists wound healing as a large surface area is presented which is quickly penetrated by 20 body fluids and goes into solution in these fluids. We believe that the product then chemically degrades to achieve more rapid absorption and enhancement of the wound healing process.

25 The overall homogeneity of the distribution of oxidised groups within the product is increased. Thus, the product has improved reactivity and accessibility to reactive sites for the purpose of binding other substances such as pharmacologically active substances to the product. The average degree of polymerisation is decreased, the distribution of the polymerisation is narrowed and the amount of cellulosic fractions are reduced. This also assists in 30 biodegradation.

The polyanhydroglucuronic acid and salts thereof may be made up of particles sized from 0.1 to 100 μm and/or fibres of from 5 to 30 μm diameter and up to 30 mm length.

- 5 Preferably the hydrolysate is let to undergo fractional coagulation by a suitable water-miscible organic solvent, the coagulated product is washed, or dehydrated, using a suitable water-miscible organic solvent, and/or converted, in an appropriate manner, for intended subsequent use.
- 10 Preferably the inorganic and/or organic salts and/or bases preferably used for hydrolysis are chlorides, sulphates, carbonates, formates, or acetates or alkali and/or alkaline earth metals, hydroxides of alkali and/or alkaline earth metals, alkylamines, or alkanolamines, in concentrations ranging from 1×10^{-3} to 5 mol/l.
- 15 Preferably the oxidative environment during hydrolysis is established by the presence of oxidative agents such as hydrogen, sodium or magnesium peroxide, peroxyacides and their salts, hypochlorites, or chlorites.

20 Detailed Description

The invention will be more clearly understood from the following description thereof given by way of example only.

- 25 The essence of the invention consists in the ability of the microdispersed polyanhydroglucuronic acid and salts thereof to form stable dispersions in physiologically indifferent liquids displaying low to zero rate of sedimentation, low viscosity of these colloid-dispersion non-aqueous systems, and no tendency to agglomerate, at concentrations of 0.5 to 15 % b/w.

Of important advantage is the fact that the physicochemical properties of the microdispersed polyanhydroglucuronic acid can be controlled to fit the dispersing liquid or mixture of liquids, thus allowing stable systems suitable as spray fillings to be prepared.

Extensive tests have shown that the microdispersed polyanhydroglucuronic acid and salts thereof prepared by controlled hydrolysis and fractionation, mostly in the form of particles smaller than the size of an erythrocyte, is capable of stimulating the activity of histiocytes and macrophages, which represents another essential advantage of the application of such substances. At the same time, they effectively arrest capillary bleeding of the wound area while getting incorporated into the fibrin net formed. Due to small size of the order of microns, the particles of the microdispersed polyanhydroglucuronic acid and salts thereof undergo, dependent on the chemical composition and physiochemical properties, relatively rapid enzymatic hydrolysis in the wound environment yielding glucose and glucuronic acid, substances inherent to living organism, as final products; in fact, histological observations indicate that they are presumably incorporated into body mucopolysaccharides. Close to neutral pH value of extracts of salts of microdispersed polyanhydroglucuronic acid also substantially contributes to their biocompatibility; no adverse secondary effects due to acidic nature have been reported in their applications.

The presence of reactive carboxyl groups in the microdispersed polyanhydroglucuronic acid and salts thereof is the basis for their ability to chemically bind substances with antibacterial effects such as e.g. derivatives of biguanid, quaternary ammonium salts, or aminosaccharide based antibiotics. Bactericidal activity is also observed for salts or complex salts of certain cations, such as Zn^{2+} , Cu^{2+} , and to a limited extent Ag^+ , with microdispersed polyanhydroglucuronic acid.

Similarly, we have observed that preparations based on the microdispersed polyanhydroglucuronic acid and salts thereof display certain insecticidal activity. This activity can be enhanced using hydrophobic reactivity of polyanhydroglucuronic acid molecules which allows to anchor, on the powder substance, non-toxic synthetic derivatives of natural pyrethrins such as pyrethroids, notably Permethrin (cis/trans isomer ratio 1:3). Another advantage of compositions according to the invention is thus represented by the possibility to combine, in a single product, hemostatic, bacteriostatic, and insecticidal function. This is important in veterinary medicine for the treatment of both traumatic and artificial lesions in e.g. sheep and cattle, in that it provides a temporary protection against microbial infection and insect attack during healing.

An example of successful combination of an antibiotic and a hemostatic may be represented by the application of neomycine ut sulfas and bacitracinum zincicum bound to a sodium/calcium salt of microdispersed polyanhydroglucuronic acid.

The main problem that had to be solved within the invention concerns the choice of dispersing liquids and propellants to be used in aerosol packaging formulations of the microdispersed polyanhydroglucuronic acid and salts thereof.

Extensive tests have surprisingly revealed that the use of organosols containing several different substituents or highly polar substituents caused the system to easily form coacervates or even to coagulate.

We have found that eg alcoholic dispersions display a relatively low stability with a rapid coagulation and/or sedimentation of particles. The stability is increased with increasing size of the aliphatic chain of the molecule, but the application of higher alcohols is limited from the physiological point of view. We have also found that the hemostatic efficacy of the microdispersed polyanhydroglucuronic acid based products in the initial phase immediately after the spray administration is reduced by the presence of water or polyhydroxycompounds such as glycerol

and its derivatives, glycols and polyglycols. Univalent alcohols such as ethanol can induce a stinging pain on application to the wound. Substances of the latter types are therefore preferably avoided in the formulation.

5 Coagulation and/or sedimentation was surprisingly equally observed in systems where a substance with low polarity has been used, but the molecule contained several different substituents giving rise to an electrostatic non-equilibrium, the Examples of these being dichlorotetrafluoroethane or trichlorofluoromethane. In contrast, low polar substances such as alkanes, C1 to C8 cycloalkanes, or their 10 fluorinated and perfluorinated derivatives, yielded stable dispersion systems with a low sedimentation rate. Examples are methane, ethane, propane, butane, isobutane, pentane, 2-methylbutane, 2-methylpropane, 2,2-dimethylpropane and the like. Substances with 3 to 5 carbon atoms such as pentane, neopentane, or a pure petrol fraction free from mercaptanes and aromatics may preferably be used 15 to reduce loss at administration, to improve fixation of the substance upon the treated area.

We have further found that the organic liquid molecule may also contain a 20 heteroatom, preferably oxygen, in the main chain without deteriorating the system stability. Such substances would involve ethers such as dimethylether, diethylether, but also perfluorinated ethers of the methoxy- or ethoxy-nonafluorobutane type.

Extensive tests have shown that the product, though involving an important 25 number of hydrophilic polar groups, can best be dispersed in low polar or non-polar liquids with a low surface tension and low relative permitivity. In contrast, we have found that liquids with higher polarity and higher surface tension tend to support agglomeration of the product particles and thus to jeopardise the correct function of the aerosol packaging. Besides the effect of microparticles with a large 30 specific surface area, the good dispersability of the microdispersed polyanhydroglucuronic acid and salts thereof may be attributed to their ability to

enter, in spite of the presence of hydrophilic groups, hydrophobic interactions with the dispersing liquids. The results indicate that stable dispersion systems can preferably be obtained using those of the above substances which display a value of the relative permitivity (dielectric constant at 25°C and 10 kHz) less than 10, preferably less than 5, and that of the surface tension less than 30mN/m, preferably less than 15mN/m. Thus the substances recommended for use involve, preferably, C₃ to C₅ alkanes, isoalkanes, or cycloalkanes, 1,1,1,2-tetrafluoroethane, dimethylether, methoxy- and ethoxy-nonafluorobutane and mixtures thereof.

10

Besides the ability to form low sedimenting dispersion systems, the overall criteria limiting the choice of suitable dispersator/propellant systems further include: physiological indifference (low toxicity, zero or minimum skin and cardiac sensitisation at exposures up to 100000 ppm, no mutagenicity and carcinogenicity, minimum solubility in water and body fluids), indifference in contact with the active substance, high volatility and low heat of evaporation, ability to fix the active substance in the first phase immediately after application on the wound surface, environmental acceptability, and cost.

15

It is difficult to draw a sharp demarcation line between the dispersing medium suitable for the microdispersed polyanhydroglucuronic acid and salts thereof and the propellant since in some cases both functions can be provided for by one and the same substance such as e.g. n-butane or isobutane. In general, the relevant substances may especially involve:

20

a) Aliphatic and alicyclic hydrocarbons with 1 to 6 carbon atoms, or aliphatic ethers, notably dimethylether, diethylether, and diisopropylether. While aliphatic hydrocarbons with 1 to 3 carbon atoms could well serve as dispersators for the microdispersed polyanhydroglucuronic acid and salts thereof when under pressure, they evaporate immediately at the output of the spray outlet and thus increase the powder dissipation on spraying and

30

insufficiently fix the powder on the wound surface. It is therefore preferable to use higher hydrocarbons such as n-butane, isobutane, n-pentane, or isopentane for the given purpose. This group may also include petrolether, pentane/isopentane fraction from petroleum distillation, or a mixture of liquid hydrocarbons currently distributed under the name of medicinal petrol, under the obvious condition of being pure enough from aromatic hydrocarbons and mercaptanes. From the ether group, dimethylether can preferably be used with respect to its suitable physicochemical characteristics.

b) Nonflammable compounds known as fluorohydrocarbons (HFC), perfluorocarbons (PFC), and recently introduced hydrofluoroethers (HFE). Compared to chlorofluorocarbons (CFC), the HFC's, PFC's and HFE's display much reduced life time in the atmosphere and zero to very low ozone-depleting potential (ODP) and global warming potential (GWP). Some may have a slightly increased toxicity and bioreactivity; however, their contact with the wound is very short due to the rapid evaporation rate. The most suitable choice with respect to the properties may be represented by 1,1,1,2-tetrafluoroethane (HFC 134a), or hydrofluoro-ethers such as methoxy-nonafluoroethane (HFE 7100) or 1,1,1,2,3,3-hexafluoro-3-methoxypropane, all of these substances being acceptable from both the physiological and environmental point of view.

Representatives of both above groups are liquids or substances liquefiable at low pressures (0.2 - 1.4 Mpa) at normal conditions. Further alternatives include:

c) Gaseous substances, which cannot be liquefied at normal conditions, but capable of being absorbed, at least partially, in the powder active substance or in the liquid dispersion system. These include notably carbon dioxide, and nitrous oxide.

d) Gaseous substances not liquefiable at normal conditions and displaying a very limited absorption ability in the liquid dispersion system, such as rare gases, air, and nitrogen.

5 All of these substances can further be suitably combined with each other to provide for an optimized function of the spray. Based on extensive testing, the preferred combinations include systems such as n-butane or n-pentane/CO₂, medicinal petrol/HFC 134a, isopentane/dimethylether, medicinal petrol/HFE 7100/HFC134a, HFE 7100/CO₂, n-pentane/HFE 7100/N₂.

10 In summary, the important fact underlying the present invention is that the polyanhydroglucuronic acid and salts thereof create stable dispersion concentrates in liquids that do not compromise the environment, displaying zero or low values of both the ODP and GWP potentials.

15 An important advantage of the aerosol packaged hemostatic according to the invention consists in the fact that the contents of the packaging can repeatedly be used without the loss of their sterility. The dosing of the active substance can accurately be directed to the wound surface where the powder gets well anchored
20 due to the relatively high speed of incidence of an indifferent dispersion in a liquid that is immiscible with the body fluids and evaporates within a few seconds.

25 Certain adverse secondary effects are reported for the above listed dispersing and propellant substances, such as weak narcotic effects or skin degreasing on contact for C5 hydrocarbons. However, no such effects have been observed during extensive application tests of the sprays according to the invention because of small applied amounts and short contact time.

An additional specific advantage can be attained when using substances listed
30 under a) above or combinations of substances listed under a) and c) above for preparing the stable dispersions of the microdispersed polyanhydroglucuronic acid

and salts thereof. Such formulations of the spray allow a simple terminal sterilisation of the finished aerosol packagings to be preformed by gamma radiation.

5 EXAMPLES

Example 1

In this example, the raw material for preparing a salt of microdispersed polyanhydroglucuronic acid were cotton linters containing 99.1 % b/w (by weight) of α -cellulose and oxidised in 60 % nitric acid with an admixture of 3.6 % nitrous acid at a temperature of 28°C in analogy with the procedure of GBP 10 709684. The resulting product contained:

carboxyl groups 13.7 % b/w

carbonyl groups 4.2 % b/w

bound nitrogen 0.48 % b/w

15

In a 3000 ml laboratory mixer, 1000 ml of water and 0.158 g of calcium acetate were heated up to 60°C and stirred at 600 rpm. After dissolution of calcium acetate, 2 g of the above defined oxidised cotton linters containing about 8 % of volatile matter were added, temperature increased to 98°C, and the mixture stirred 20 at 2800 rpm for 15 minutes while maintaining the temperature. The temperature was then decreased back to 60°C, pH adjusted to 8.5 by adding sodium hydroxide solution, 25 g of 30% hydrogen peroxide were added, and the hydrolysis continued at the reduced temperature for another 15 minutes. Subsequently the reaction system was cooled down to 40°C, stirring reduced to 300 rpm, and 1500 25 ml of 92% ethanol were added stepwise during about 10 minutes. The resulting colloid dispersion solution was then filtered, the residue was dispersed into 50%

water-ethanol mixture and allowed to stand for one hour. After another filtration the residue was redispersated into 100 ml of isopropanol and allowed to stand for 6 hours. The same procedure was repeated once more, and then the product was filtered and dried in a vacuum drier at a temperature of 40°C.

5

An analysis of the product obtained yielded:

loss on drying 1.25 % b/w
carboxyl group content 16.8 % b/w
carbonyl groups 0.5 % b/w
bound nitrogen content 0.13 % b/w
calcium content 2.1 % b/w
sodium content 5.2 % b/w
particle size 2 to 5 μ m
specific surface area 98 m^2/g
Molecular weight 6×10^4 Daltons

10 The product can be used directly as a haemostatic powder or as a component of an aerosol powder spray.

Example 2

15 A haemostatic composition in pressurised aerosol packaging has been prepared using stable microdispersed polyanhydroglucuronic acid in the form of calcium/sodium salt as described in Example 1 above. The equipment used included a stainless steel 1000 litre mixer with a propeller stirrer, a stainless steel 30 litre/min metering pump with inner circulation, and an aerosol filling machine

(Pamasol type) with one filling head for the dispersion concentrate and two filling heads for the propellant.

5 The bulk substance used in this example was a calcium/sodium salt of microdispersed polyanhydroglucuronic acid having the following characteristics:

particle size 20 - 60 µm	2 % b/w
10 - 20 µm	32 % b/w
≤ 10 µm	66 % b/w
specific surface area	105 m ² /g
carboxyl group content (total)	20.2 % b/w
carboxyl group content (uronic)	18.2 % b/w
free formaldehyde	0 % b/w
foreign particles	0 % b/w
calcium content	3.9 % b/w
sodium content	5.6 % b/w
bound nitrogen content	0.02 % b/w

10 Chlorohexidine hydrochloride (Ferrosan) in concentration of 0.1 % b/w was added as a bacteriostatic adjuvant. The dispergation/propellant system involved a liquid hydrocarbon mixture (known as medicinal petrol) with density of 652 kg/m³, boiling point 55°C, and residue after evaporation < 2 ppm, and 1,1,1,2-tetrafluoroethane (HFC 134a).

15 40 kg of the active substance was placed into the mixer, 150 litres of the liquid hydrocarbon mixture added, and the system stirred at 600 rpm for 5 minutes. After addition of 1 kg of chlorohexidine hydrochloride and of another 250 litres of the liquid hydrocarbon mixture, the system was further stirred until a uniform dispersion was obtained. The metering pump was used to dose the dispersion via the filling head of the filling machine into aerosol cans of 80 ml nominal volume.

in doses of 31 g per can. After inserting a suitable valve, another filling head was used to add 18 g per can of the 1,1,1,2-tetrafluoroethane propellant.

5 The finished spray can be used for treatment of bleeding wounds by both the professional or a layman.

Example 3

The same equipment was used as in Example 2. The active substance consisted of
10 two components, MDOC1 with the same characteristics as in Example 2, and MDOC2 involving a zinc/calcium/sodium salt of microdispersed polyanhydroglucuronic acid having the following properties:

carboxyl group content	19.5 % b/w
free formaldehyde	0 % b/w
zinc content	9.5 % b/w
calcium content	3.9 % b/w
sodium content	5.6 % b/w
bound nitrogen content	0 % b/w

15 Neomycinum ut sulfas and Bacitracinum zincicum were used as antibacterial adjuvants, n-pentane having density of 625 kg/m³, and boiling point 36°C, as the dispersator, and carbon dioxide (edible grade quality) as the propellant.

20 38.8 kg of MDOC1 and 1.2 kg of MDOC2 was placed into the mixer together with 0.132 kg of Neomycinum ut sulfas and 0.143 kg (10^7 IU) of Bacitracinum zincicum, 200 litres of n-pentane added, and the system thoroughly stirred.

Another 200 litres of n-pentane were then added and stirred for another 10 minutes. Aerosol cans of 80 ml nominal volume were then filled in doses of 31 g per can, and, after inserting the valves, another filling head was used to pressurise the can by addition of 2 g of compressed carbon dioxide.

The finished spray can be used for professional treatment of bleeding wounds and lesions.

5 Example 4

A thoroughly homogenised uniform powder mixture of microdispersed polyanhydroglucuronic acid in the form of magnesium/calcium/sodium and zinc/calcium/sodium salts in the mass ratio of 32:1 is filled into aerosol cans of 10 210 ml nominal volume in doses of 8 g per can on a powder dosing machine (Bosch). Upon closing the can with an appropriate valve, the can is pressurised on the aerosol filling machine by adding 20 g of n-butane and 30 g of dimethylether. Finished and gamma sterilised sprays then can be used for treatment of smaller burns or scalds. It can also be applied in e.g. urological or gynecological surgery.

Example 5

5 Into the mixer as described in Example 2, 25 kg of calcium/sodium salt of microdispersed polyanhydroglucuronic acid (Example 1), 5.0 kg of calcium stearate, 0.4 kg of chlorohexidine hydrochloride, and 7.7 kg of Permethrin with cis/trans ratio of 25:75 (ICI Plant Protection) are successively placed. After addition of 400 litres of n-pentane and 99 kg of methoxy-nonafluorobutane (HFE 10 7100), the contents of the mixer are stirred for 15 minutes. The uniform dispersion is then filled into aerosol cans of 210 ml nominal volume in doses of 110 g per can on the filling machine and closed with an appropriate valve. Another filling head 15 is then used to add 50 g per can of dimethylether.

15 The finished spray is designed for use in veterinary practice for treatment of wounds and lesions in e.g. sheep and cattle, simultaneously providing a temporary protection against microbial and/or insect attack.

Example 6

20 A hydrophilised adduct (MDOC-ACV) of 9-[(2-hydroxy-methoxy)-methyl]-guanin (acyclovir) and a calcium/sodium salt of microdispersed polyanhydroglucuronic acid as described in Example 1, the content of acyclovir in the MDOC-ACV adduct being 50.5 % b/w.

25 A homogenised mixture of the adduct, the magnesium/calcium/sodium salt of microdispersed polyanhydroglucuronic acid according to Example 1, and the zinc/calcium/sodium salt thereof according to Example 2 in the mass ratio of 8.7 : 0.3 : 1.0 is filled into aerosol cans of 120 ml nominal volume in doses of 4 g per can on a powder dosing machine (Bosch). Upon closing the can with an appropriate valve, the aerosol filling machine is used to pressurise the can by 30 adding 25 g of 2,2-dimethylpropane (neopentane) with a density of 625 kg/m³.

and boiling point 9.6°C, on filling head 1, and 23 g of dimethylether with a density of 668 kg/m³.

The finished spray is packed and sterilised by gamma radiation with a dose of 25
5 kGy and used as a dusting powder in the treatment of e.g. herpes zoster, enabling an easy application and good efficacy even in hairy areas of the body.

The invention is not limited to the embodiments hereinbefore described which may be varied in detail.

CLAIMS

1. Haemostatically active aerosol composition comprising from 0.005 to 0.25 parts by weight of microdispersed polyanhydroglucuronic acid and/or acceptable salts thereof and from 0.75 to 0.005 parts by weight of a suitable dispersing/propellant system.
2. An aerosol composition as claimed in claim 1 wherein the dispersing/propellant system includes liquids which are non-polar or of low polarity.
3. An aerosol composition as claimed in claim 2 wherein the liquids have a surface tension of less than 30 mN/M and a permitivity at 10 kilohertz of less than 10.
4. An aerosol composition as claimed in claim 3 wherein the surface tension is less than 18 mN/M.
5. An aerosol composition as claimed in claim 3 or 4 wherein the permitivity at 10 kilohertz is less than 5.
6. An aerosol composition as claimed in any preceding claim wherein the dispersing/propellant system does not include water or polyhydroxy compounds.
7. An aerosol composition as claimed in any preceding claim wherein the system does not include a univalent alcohol.
8. An aerosol composition as claimed in any of claims 1 to 7 wherein the dispersing/propellant system is selected from one or more of alkanes, C1 to C8 cycloalkanes, fluorinated, or perfluorinated derivatives thereof.

9. An aerosol composition as claimed in claim 8 wherein the dispergating/propellant system is selected from one or more of methane, ethane, propane, butane, isobutane, pentane, 2-methylbutane, 2-methylpropane, and 2,2-dimethylpropane.
5
10. An aerosol composition as claimed in claim 8 or 9 wherein the system is selected from one or more of C₃ to C₅ alkanes, cycloalkanes, derivatives thereof and a petrol fraction substantially free from mercaptans and aromatics.
10
11. An aerosol composition as claimed in any preceding claim wherein the dispergating/propellant system includes a heteroatom in the main chain.
15
12. An aerosol composition as claimed in claim 11 wherein the heteroatom is oxygen.
13. An aerosol composition as claimed in claim 12 wherein the system comprises ethers and perfluorinated derivatives thereof.
20
14. An aerosol composition as claimed in claim 13 wherein the system is selected from one or more of dimethylether, diethylether, and perfluorinated ethers, especially methoxy- or ethoxy- nonafluorobutane.
15. An aerosol composition as claimed in any of claims 1 to 14 wherein the system comprises one or more of C₃ to C₅ alkanes, isoalkanes, or cycloalkanes, 1,1,1,2-tetrafluoroethane, dimethylether, methoxy- and ethoxy- nonafluorobutane.
25
16. An aerosol composition as claimed in any of claims 1 to 7 preceding claim wherein the system includes one or more aliphatic hydrocarbons, alicyclic hydrocarbons of C1 to C6, aliphatic ethers or mixtures thereof.
30

17. An aerosol composition as claimed in claim 16 wherein the aliphatic hydrocarbons are selected from those having from 4 to 6 carbon atoms.
- 5 18. An aerosol composition a claimed in claim 16 or 17 wherein the aliphatic ethers are selected from dimethylether, diethylether and diisopropylether.
- 10 19. An aerosol composition as claimed in claim 18 wherein the ether is dimethylether.
- 20 20. An aerosol composition as claimed in any preceding claim wherein the system includes one or more hydrofluorocarbons, perfluorocarbons or hydrofluroethers.
- 15 21. An aerosol composition as claimed in claim 20 wherein the system includes one or more hydrofluorocarbons or hydrofluoroethers.
22. An aerosol composition as claimed in claim 21 wherein the hydrofluorocarbon is 1,1,1,2-tetrafluoroethane (HFC 134a).
- 20 23. An aerosol composition as claimed in claim 21 wherein the hydrofluoroethers are selected from methoxy nonafluoroethane (HFE7100) and 1,1,1,2,3,3-hexafluoro-3-methoxypropane.
- 25 24. An aerosol composition as claimed in any preceding claim wherein the system includes a gaseous substance which is not liquifiable at normal aerosol operating conditions.
- 30 25. An aerosol composition as claimed in claim 24 wherein the gaseous substances are at least partially absorbable by the microdispersed polyanhydroglucuronic acid and/or salts thereof.

26. An aerosol composition as claimed in claim 25 wherein the gaseous substance is selected from either carbon dioxide and/or nitrous oxide.
- 5 27. An aerosol composition as claimed in claim 24 wherein the gaseous substance has limited absorbability in the system.
28. An aerosol composition as claimed in claim 27 wherein the gaseous substance is selected from one or more of rare gases, air and nitrogen.
- 10 29. An aerosol composition as claimed in any preceding claim wherein the system includes n-butane and carbon dioxide.
- 15 30. An aerosol composition as claimed in any of claims 1 to 29 wherein the system includes n-pentane and carbon dioxide.
31. An aerosol composition as claimed in any of claims 1 to 29 wherein the system includes medicinal petrol and HFC 134a.
- 20 32. An aerosol composition as claimed in any of claims 1 to 29 wherein the system includes isopentane and dimethylether.
33. An aerosol composition as claimed in any of claims 1 to 29 wherein the system includes medicinal petrol, HFE 7100 and HFC 134a.
- 25 34. An aerosol composition as claimed in any of claims 1 to 29 wherein the system includes HFE 7100 and CO₂.
35. An aerosol composition as claimed in any of claims 1 to 29 wherein the system includes n-pentane, HFE 7100 and N₂.

36. An aerosol composition as claimed in any preceding claim wherein the composition includes at least one pharmaceutically acceptable adjuvant.
37. An aerosol composition as claimed in claim 36 wherein the adjuvant is selected from one or more substances having suitable anti-microbial, anti-viral, anti-mycotic and/or anti-parasitic effects.
38. An aerosol composition as claimed in any preceding claim wherein the stable microdispersed polyanhydroglucuronic acid and/or salts thereof are in the form of particles having a size from 0.1 to 80 μm .
39. An aerosol composition as claimed in claim 38 wherein the stable microdispersed polyanhydroglucuronic acid and/or salts thereof are in the form of particles having a size of from 5 to 15 μm .
40. An aerosol composition as claimed in any preceding claim wherein the polyanhydroglucuronic salts are selected from calcium, magnesium, sodium and/or potassium salts.
41. An aerosol composition as claimed in any preceding claim wherein the microdispersed polyanhydroglucuronic acid and salts thereof contain in their polymeric chain from 8 to 30 per cent by weight of carboxyl groups, at least 80 per cent by weight of these groups being of the uronic type, at most 5 per cent by weight of carbonyl groups, and at most 0.5 per cent by weight of bound nitrogen.
42. An aerosol composition as claimed in claim 33 wherein the polyanhydroglucuronic acid and salts thereof contain in their polymeric chain at most 0.2 per cent by weight of bound nitrogen.

43. An aerosol composition as claimed in claim 41 or 42 wherein the polyanhydroglucuronic acid and salts thereof have a molecular mass of the polymeric chain of from 1×10^3 to 3×10^5 Daltons.
- 5 44. An aerosol composition as claimed in any of claims 41 to 43 wherein the polyanhydroglucuronic acid and salts thereof have a molecular mass of the polymeric chain of from 5×10^3 to 1.5×10^5 Daltons.
- 10 45. An aerosol composition as claimed in any of claims 41 to 44 wherein the content of carboxyl groups is in the range of from 12 to 26 per cent by weight, at least 95 per cent of these groups being of the uronic type.
- 15 46. An aerosol composition as claimed in any of claims 41 to 45 wherein the polymeric chain contains at most 1 per cent by weight of carbonyl groups.
47. An aerosol composition as claimed in any of claims 41 to 46 wherein the carbonyl groups are intra- and intermolecular 2,6 and 3,6 hemiacetals, 2,4-hemialdals and C2-C3 aldehydes.
- 20 48. An aerosol composition as claimed in any preceding claim wherein the polyanhydroglucuronic acid and/or salts thereof are prepared by a method wherein a polyanhydroglucuronic acid-containing material is subjected to partial or complete hydrolysis and neutralisation in an oxidative environment, the hydrolysate undergoing fractional coagulation to form a stable microdispersed product.
- 25 49. An aerosol composition as claimed in claim 48 wherein the hydrolysis is carried out in an aqueous solution of inorganic and/or organic salts and/or bases.

50. An aerosol composition as claimed in claim 49 wherein the inorganic and/or organic salts and/or bases used for hydrolysis are chlorides, sulphates, carbonates, formates, or acetates of alkali and/or alkaline earth metals, hydroxides of alkali and/or alkaline earth metals, alkylamines, or alkanolamines, in concentrations ranging from 1 to 10^3 to 5 mol/l.
- 5 51. An aerosol composition as claimed in any of claims 48 to 50 wherein the oxidative environment during hydrolysis is established by the presence of agents selected from one or more of hydrogen, sodium or magnesium peroxide, peroxyacides and their salts, hypochlorites and chlorites.
- 10 52. A composition as claimed in any of claims 48 to 51 wherein the hydrolysate undergoes fractional distillation by a suitable water-miscible organic solvent.
- 15 53. A composition as claimed in claim 52 wherein the coagulated product is washed, or dehydrated, using a suitable water-miscible organic solvent, and/or converted, in an appropriate manner.
- 20 54. An aerosol composition as claimed in any of claims 48 to 53 wherein the procedure is carried out at a pH of from 1 to 12.
55. An aerosol composition as claimed in any of claims 48 to 54 wherein the procedure is carried out at a temperature of from 0 to 100°C.
- 25 56. An aerosol composition as claimed in any of claims 48 to 55 wherein the polyanhydroglucuronic acid-containing material is obtained by oxidation of a suitable polysaccharide, such as native or regenerated cellulose or starch.

57. A haemostatically active aerosol composition substantially as hereinbefore described with reference to the Examples.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IE 98/00003

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 A61K9/12 A61K31/19 A61K31/70 A61K31/715 A61L25/00

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEMICAL ABSTRACTS, vol. 117, no. 1, 4 January 1993 Columbus, Ohio, US; abstract no. 578301, KASPAR: "MICROEMBOLIZATION AGENT" XP002062982 see abstract & CS 272 002 B (CZECH.) 26 September 1991 --- CHEMICAL ABSTRACTS, vol. 106, no. 26, 29 June 1987 Columbus, Ohio, US; abstract no. 219652, BLAZICEK ET AL.: "HEMOSTATIC SUBSTANCE" XP002062983 see abstract & CS 235 108 B (CZECH.) 15 February 1987 --- -/-	1,2,6-8, 36-40,57
Y		1,2,6-8, 36-40,57

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

3

Date of the actual completion of the international search

27 April 1998

Date of mailing of the international search report

14/05/1998

Name and mailing address of the ISA
 European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl
 Fax: (+31-70) 340-3016

Authorized officer

Fischer, W

INTERNATIONAL SEARCH REPORT

Inte: National Application No

PCT/IE 98/00003

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>CHEMICAL ABSTRACTS, vol. 121, no. 1, 2 January 1995 Columbus, Ohio, US; abstract no. 570118, V. A. STELMAH ET AL.: "POLYCAPRAN. EVALUATION OF HEMOSTATIC ACTION" XP002062984 see abstract & VESTN. BELORUSS. GOS. UNIV., 1993, pages 43-45,</p> <p>---</p> <p>PATENT ABSTRACTS OF JAPAN vol. 008, no. 236 (C-249), 30 October 1984 & JP 59 116213 A (UNITIKA KK), 5 July 1984, see abstract</p> <p>---</p> <p>GB 1 254 534 A (WALLACE, CAMERON & COMPANY LTD.) 24 November 1971 see the whole document</p> <p>-----</p>	1,2,6-8, 36-40,57
Y		1,2,6-8, 36-40,57
Y		1,2,6-8, 36-40,57

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IE 98/00003

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 1254534 A	24-11-71	NONE	